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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/308,829	07/14/99	SCHLIEVERT	P 600.347USWO

EXAMINER	
HINES, J	
ART UNIT	PAPER NUMBER
1645	14

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DATE MAILED: 02/08/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/308,829	Schllevert et al.
Examiner	**Group Art Unit**
Ja-Na Hln s	1645

☒ Responsive to communication(s) filed on *Nov 20, 2000*

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-23* is/are pending in the applicat

Of the above, claim(s) *2, 13, and 14* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 3-12, and 15-23* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Amendment Entry

1. Amendments have been entered as filed on November 20, 2000. Claims 2 and 13-14 were canceled. Claims 1, 3-5, 7, 9 and 17 have been amended. Claims 18-23 are newly added. Claims 1, 3-12 and 15-23 are pending in this office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1, 3-12 and 15-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabled for a Streptococcal pyrogenic exotoxin type C (SPE-C) mutant with specifically named amino acid substitutions in a Beta barrel of the B-subunit or a N-terminal alpha helix, does not reasonably provide enablement for a Streptococcal pyrogenic exotoxin type C (SPE-C) mutant with any amino acid substitutions in the Beta barrel of the B-subunit or a N-terminal alpha helix, whereby the amino acid sequence is altered by any substitution of one more amino acids. The specification does not enable any person skilled in the art to which it pertains,

or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Claim 1 recites that the mutant can be obtained by any substitution of one or more amino acids in the Beta-barrel or N-terminal alpha helix, however that specification only provides guidance to specific amino acids and does not teach any amino acid substitution may be changed without causing a detrimental effect to the SPE-C toxin to be produced. The claim broadly recites an amino acid substitution, therefore any amino acid is being claimed, and no specific substitution is recited, if all the amino acids are substituted the resulting mutant SPE-C could result in a mutant toxin not taught or enabled by the specification.

Claim 19 recites that the mutant can be obtained by substituting one to six amino acids at positions 12, 15, 17, 35 or 38, however the claims does not teach what the amino acids can be substituted with. Further, the claims do not recite whether the substitution needs to be a conservative substitution. The specification only provides guidance to specific amino acids and does not teach any amino acid substitution may be changed without causing a detrimental effect to the SPE-C toxin to be produced even though the positions are recited. The claim broadly recites an amino acid substitution, therefore any amino acid is being claimed, and no specific substitution is recited, if all the amino acids at the recited positions are substituted the resulting mutant SPE-C could result in a mutant toxin not taught or enabled by the specification.

The specification does not provide substantive evidence that the claimed vaccines which broadly teach an amino acid substitution is capable of inducing protective immunity. This demonstration is required for the skilled artisan to be able to use the claimed vaccines for their intended purpose of preventing Streptococcus infections. Without this demonstration, the skilled artisan would not be able to reasonably predict the outcome of the administration of the claimed vaccines, i.e. would not be able to accurately predict if protective immunity has been induced by any mutant of SPE-C.

Thomas E. Creighton, in his book, "Proteins: Structures and Molecular Properties, 1984", (pages 314-315) teaches that variation of the primary structure of a protein can result in an instable molecule. He teaches that a single amino acid change can cause a mutant hemoglobin to have lower stabilities due to any of several causes:

1) alteration of close-packing of the interior; loss of one group that normally participates in a hydrogen bond or salt bridge;

2) the introduction of a charged or polar group into the interior or the insertion into a helical region of a Proline residue, which must distort the alpha-helix;

3) while sometimes radical changes of surface groups, even introduction of a non-polar side chain- have no great effect on stability.

Thomas E. Creighton, in his book "Protein structure: A Practical Approach, 1989; pages 184-186" teaches that present day site directed mutagenesis of a gene allows any amino acid in a protein sequence to be changed to any other, as well as introducing deletions and insertions. The

reference goes on to teach that it is difficult to know which amino acid to change and which is the best residue to substitute for the desired functional and structural effect.

Nosoh, Y. et al in "Protein Stability and Stabilization through Protein Engineering, 1991" (chapter 7, page 197, second paragraph) adds support to Thomas E. Creighton, by teaching that results so far accumulated on the stability and stabilization of proteins appear to indicate that the strategy for stabilizing proteins differ from protein to protein and that any generalized mechanisms for protein stability have not yet been presented.

The substitution of any amino acid in the recited location within the mutant SPE-C would not predictably result in a stable molecule. The specification only teaches the use of specific amino acids in specific locations which result in stable variations. No working examples are shown containing the missing information. Without such information, one of skill in the art could not predict which deletions, substitutions or insertions or any combination thereof would result in the desired stable, active protein. Accordingly, one of skill in the art would be required to perform undue experimentation to use any amino acid at any location to produce a stable SPE-C toxin. Therefore, one skilled in the art could not make and/or use the invention without undue experimentation.

3. Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The recitation of " substantially enhance endotoxin shock" in claim 10 is vague. The

term substantially is not defined by the claims or specification such that one skilled in the art would be able to ascertain what level "substantially" would represent. Further, it is unclear how to determine whether a mutant does not substantially enhance endotoxin shock and correspond to the wild type toxin.

Response to Amendment

4. Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for specific amino acid mutations of Streptococcal pyrogenic exotoxin type C (SPE-C), does not reasonably provide enablement for altering the amino acid sequence by any insertion, deletion or substitution of one more amino acid is withdrawn in view of applicants amendments.

5. Claims 1-10, 13-14 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goshorn et al., in view of Hartwig et al., is withdrawn in view of applicants amendments.

6. Claims 11-12 and 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goshorn et al., in view of Hartwig et al., in further view of Leung et al., is withdrawn in view of applicants amendments.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MEP. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is (703) 305-0487. The examiner can normally be reached on Monday through Thursday from 6:30am to 4:00pm . The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Ja-Na Hines

February 2, 2001

2/7/01

JENNIFER GRASER
PATENT EXAMINER